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Review

Understanding antimicrobial pharmacokinetics in critically ill patients to optimize antimicrobial therapy: A narrative review

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ABSTRACT

Effective treatment of sepsis not only demands prompt administration of appropriate antimicrobials but also requires precise dosing to enhance the likelihood of patient survival. Adequate dosing refers to the administration of doses that yield therapeutic drug concentrations at the infection site. This ensures a favorable clinical and microbiological response while avoiding antibiotic-related toxicity. Therapeutic drug monitoring (TDM) is the recommended approach for attaining these goals. However, TDM is not universally available in all intensive care units (ICUs) and for all antimicrobial agents. In the absence of TDM, healthcare practitioners need to rely on several factors to make informed dosing decisions. These include the patient's clinical condition, causative pathogen, impact of organ dysfunction (requiring extracorporeal therapies), and physicochemical properties of the antimicrobials. In this context, the pharmacokinetics of antimicrobials vary considerably between different critically ill patients and within the same patient over the course of ICU stay. This variability underscores the need for individualized dosing. This review aimed to describe the main pathophysiological changes observed in critically ill patients and their impact on antimicrobial drug dosing decisions. It also aimed to provide essential practical recommendations that may aid clinicians in optimizing antimicrobial therapy among critically ill patients.

Introduction

The treatment of critically ill patients poses unique challenges to healthcare providers, particularly during the management of infections. In this context, antibiotics play a pivotal role in combating infections and improving patient outcomes. However, the pharmacokinetics (PK) and pharmacodynamics (PD) of antibiotics in these patients differ significantly from those in the general population. Understanding these pathophysiological alterations are crucial to the optimization of antibiotic therapy. Factors such as altered organ function, changes in tissue perfusion, and variations in fluid balance can significantly affect drug absorption, distribution, metabolism, and elimination. Traditional dosing regimens may therefore achieve inadequate therapeutic drug concentrations in critically ill patients. In addition, the pathophysiological condition in these patients may affect the PD of antibiotics. The achievement of optimal bactericidal effect and minimization of antibiotic resistance requires a thorough understanding of the mechanisms via which the drug interacts with the pathogen. This involves several considerations including the mechanism of action of the antibiotic, minimal inhibitory concentration (MIC) of the infecting organism, and duration of exposure.

This narrative review provides a comprehensive overview of the pathophysiological alterations occurring in critically ill patients, the main factors that influence antibiotic PK and PD in this population, challenges in dosing optimization, and strategies that healthcare providers may employ to ensure effective antibiotic therapy.

Pathophysiological Alterations in Intensive Care Unit (ICU) Patients

Drug PK may be significantly affected in the presence of pathophysiological changes that occur during critical illness. In conjunction with the strategies used for the early management of critical illness (such as administration of fluids and vasopressors), the development of systemic inflammatory response syn-

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drome (in the setting of major surgery, trauma, burns, or sepsis) significantly affects the two major PK parameters related to drug dosing, namely, the volume of distribution (Vd) and drug clearance (CL).[1–3]

Changes in Vd

The development of increased vascular permeability and edema during sepsis may result in substantial transfer of fluids from the intravascular compartment to the interstitial space; this increases the Vd of antimicrobial drugs. Notably, the initial management of critical illnesses, which often involves the administration of fluids, inotropes, and vasopressors, exacerbates this phenomenon. Hydrophilic drugs (particularly β-lactams, aminoglycosides, and vancomycin) which have a low Vd are more susceptible to the impact of these pathophysiological changes. Factors such as the presence of pleural effusion, ascites, and surgical drains may further expand the Vd of these drugs.

Hypoalbuminemia is commonly found in critically ill patients, and baseline serum albumin concentrations fall below 25 g/L in over 40% of ICU patients.[4] This may lead to alterations in drug-albumin binding, particularly for drugs that are highly bound to plasma proteins and are commonly used in the ICU setting; these include ceftriaxone, cefazolin, ertapenem, echinocandins, and teicoplanin. These drugs demonstrate considerably high plasma protein binding, with levels of up to 95%. Hypoalbuminemia may therefore lead to an increase in the fraction of unbound drug in the blood; this fraction is freely distributed into tissues, further extending the Vd of these drugs. Increases in the Vd are likely to decrease the maximum plasma/serum drug concentration (Cmax) and total drug concentrations over time. This may lead to potential underdosing and provide sub-therapeutic concentrations. An increase in the dose may be necessary during the initial phase of treatment, and adjustments need to be made based on unbound drug levels.[5,6]

Changes in drug CL

Worsening of organ function with progression of the illness may lead to multiple organ dysfunction syndrome. In this context, impaired perfusion of the peripheral organs (such as the gastrointestinal tract and kidney) may hinder drug absorption and elimination. In addition, a reduction in hepatic blood flow may lead to a decrease in drug metabolism; this is particularly relevant to drugs that undergo significant hepatic metabolism and have a high extraction ratio. Chronic liver failure may further impact hepatic drug metabolism, and result in decreased drug dosing; in this context, the dosing of echinocandins is reduced in severe cirrhosis.[7]

Altered drug CL is a key determinant of maintenance dose (MD) adjustments in critically ill patients. Enhanced renal elimination, also known as augmented renal clearance (ARC), is an important phenomenon observed in critically ill patients, and may significantly affect drug PK.[8] In clinical practice, a measured urinary creatinine clearance (CrCl) value of $\geq$130 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ is most commonly used as the cut-off value for defining ARC. Hyperdynamic states resulting from fluid resuscitation and vasopressor administration may lead to increased blood flow in major organs such as the kidney, and thereby increase renal elimination. The concept of renal function reserve has also been used to explain the underlying mechanism for ARC. This concept refers to the ability of the kidneys to increase the glomerular filtration rate via nephron recruitment, increased renal blood flow, and hyperfiltration; it is seen in certain conditions such as systemic inflammatory response syndrome, trauma, burns, and pregnancy. In populations with neurological disorders, brain–kidney crosstalk has been hypothesized to be an underlying mechanism. Notably, autonomic dysregulation may result in variable alterations in both renal and cerebral perfusion, and the mutual crosstalk may enhance the overall regulation of perfusion in both organs.[9] Risk factors for the development of ARC include young age, sepsis, trauma, surgery or neurosurgery, febrile neutropenia, and burn injuries.[10] Hydrophilic drugs that are primarily cleared via the kidney may exhibit substantial changes in CL in the presence of ARC. In their study on a cohort of critically ill patients, Udy et al.[11] demonstrated a strong association between augmented creatinine CL and β-lactam underexposure. Several observational studies have also reported similar results in cases of traumatic brain injury and sepsis.[12–14]

In this context, a retrospective single-center study on critically ill patients (who were treated for hospital-acquired or ventilator-associated pneumonia [VAP]) found high-dose β-lactam regimens to be associated with improved outcomes (lower rate of therapeutic failure and recurrences) without an increase in adverse events.[15] Notably, dosing recommendations for ARC have been recently added to the package insert of new antibiotic drugs.

The methods used to assess the glomerular filtration rate warrant particular consideration. The Cockroft-Gault, Chronic Kidney Disease Epidemiology Collaboration, and Modification of Diet in Renal disease equations have been shown to underestimate renal function in critically ill patients. It is therefore essential to evaluate the measured CrCl on a daily basis to better identify ARC in patients receiving hydrophilic antibiotics (e.g., β-lactams, vancomycin, or aminoglycosides).[16–18] In this context, a recent study found that most patients who developed ARC in the cohort presented with an episode within the first week of admission; in addition, the condition developed within 3 days in half of the cases.[19] The duration of ARC varied widely, with a median and maximum time frame of 5 days and more than 1 month, respectively.[19]

Notably, altered renal elimination may also lead to varying degrees of renal impairment.

More than 50% of patients hospitalized in ICUs suffer from acute kidney injury and 20%–25% of affected individuals require renal replacement therapy (RRT) during the first week.[20] In this context, antimicrobial drug dosing is considerably more complex in patients with renal impairment. The administration of extracorporeal therapies such as RRT further adds to complexities in interpreting or predicting antimicrobial PK.[21,22] In this setting, changes to the PK depend on specific characteristics of the extracorporeal circuit, such as membrane permeability, intensity of therapy, and physicochemical properties of the drug itself (including the molecular size, degree of ionization, extent of protein binding, and hydro- or lipophilicity).[21] Residual renal function, which also contributes to drug excretion, may be an additional confounder during the calculation of optimal drug dosing in this setting.[23] As antibiotic concentrations vary widely within and between critically ill patients who receive

RRT, the selection of optimal empirical antimicrobial regimens is a complex clinical challenge in such cases. In this context, a large prospective, observational, multinational PK study demonstrated considerable variability (4–8-fold) in antibiotic dosing regimens and RRT prescriptions.[24] Median trough concentrations for meropenem and piperacillin were found to be mostly above (i.e., 12.1 mg/L and 78.6 mg/L, respectively) the recommended targets for drug efficacy (i.e., 2 mg/L and 16 mg/L, respectively). Overall, 4%–5% of cases demonstrated insufficient drug levels and 25%–35% of treated patients had excess concentrations (and were therefore at risk of potential toxicity). In a previous study on patients receiving RRT, those who were administered unadjusted regimens (similar to those used in patients with normal renal function) of broad-spectrum β-lactams showed excess levels of the drug.[25] Notably, renal impairment has been identified to be a risk factor for neurotoxicity in patients receiving unadjusted dosing regimens.[26] Alternative antimicrobials with low renal or continuous RRT-related CL should be considered where possible to limit the risk of inappropriate antimicrobial drug dosing in such settings.

Changes in drug absorption

Altered drug absorption has been previously reported in critically ill patients.[27] However, there are no clear recommendations for the management of those alterations. Critical illnesses may affect the gastrointestinal tract and lead to a decrease in intestinal peristalsis, mucosal impairment, and altered drug metabolism.[28] Enteric drug absorption and availability are difficult to predict, mainly due to fluctuations in gastric pH, loss of enteric architecture, and decreased enzymatic activity. In addition, the delay in gastric emptying extends the time needed to achieve maximum concentrations of the antibiotic. The impact of these pathophysiological alterations is illustrated by the significant decrease in the absorption of antibiotics such as ciprofloxacin in ICU patients.[29]

Changes in tissue penetration

The transport of antibiotics to tissues and subsequent distribution within tissues and cells depends on various factors including the characteristics of the drug itself, patient characteristics (e.g., obesity), disease severity, and target tissues.

Notably, different antimicrobial drugs demonstrate altered tissue penetration in critically ill patients.[30–33] As reported in the literature, the extent of these alterations varies widely among different tissues and organs.[34] In the presence of sepsis, the microcirculatory blood flow may be significantly impaired due to endothelial dysfunction and the presence of microthrombi, which decrease tissue perfusion. These alterations may lead to suboptimal antibiotic exposure at the site of infection and thereby to potential therapeutic failure, emergence of resistance, and higher morbidity.[30] Suboptimal tissue concentrations may even be found in patients with adequate plasma concentrations, as the antibiotic concentrations in plasma do not accurately reflect those in infected tissue.[31] Interestingly, clinical scoring systems such as the tissue penetration prediction score have been proposed for predicting tissue penetration of antimicrobials.[35] The main factors found to correlate with tissue penetration include oxygen saturation, serum lactate levels, and the dose per time unit of norepinephrine.[35] Although the tissue/plasma penetration ratio of antimicrobials may be an important factor for the selection of the most suitable treatment, there is currently no conclusive evidence to support the use of clinical scores for adjusting antibiotic dosing regimens. In addition, the limited availability of data pertaining to tissue penetration precludes their use in guiding antimicrobial dosing.

Changes due to extracorporeal therapies

Extracorporeal membrane oxygenation (ECMO) is an advanced life support system that is used in patients with life-threatening respiratory or cardiac failure. It provides cardiopulmonary support and can serve as a bridge to recovery, lung or heart transplantation, or the implantation of long-term ventricular assist devices. Studies have evaluated PK determinants during ECMO, and particularly the impact of the ECMO circuit on drug distribution and elimination.[36] The ECMO circuit consists of a blood pump, oxygenator, heat exchanger, and tubing; it can sequester drugs, alter apparent Vd, and affect drug CL. The degree of drug sequestration depends on physicochemical properties (lipophilicity and protein binding) and circuit factors (membrane surface area, type of tubing, oxygenator used, and priming solution), and newer technologies offer reduced risks.[37,38] Changes in apparent Vd are influenced by critical illness-related factors; the addition of an ECMO circuit leads to drug sequestration and hemodilution from the priming solution. Hemodilution is expected to have less impact on drugs with a large apparent Vd (e.g., quinolones) than on those with low Vd (e.g., β-lactams and aminoglycosides). Drug CL is generally decreased during ECMO due to reduced renal and hepatic perfusion. Estimating PK parameters during combined ECMO and RRT is therefore considerably challenging. In this context, almost half of the patients who receive ECMO require RRT; the presence of two extracorporeal circuits further adds to the complexity of drug PK.[39] An integrated approach involving mechanistic *ex vivo* experiments, animal models, and clinical studies has been employed to guide drug dosing optimization in patients receiving ECMO.[39–45]

Applying PK/PD Approaches to Optimize Antimicrobial Therapy

PK/PD targets for critically ill patients

PK/PD targets can be expressed as the Cmax/MIC, %T > MIC, or area under the curve (AUC)/MIC, depending on whether the antibiotic exhibits dose-, time-, or AUC-dependent killing. The optimal PK/PD target for guiding β-lactam dosing remains unclear. In critically ill patients, 100% of time where the free concentration is above the MIC (100% fT > MIC) is often suggested as a therapeutic target for β-lactams.[46,47] More aggressive β-lactam targets (i.e., 4–5 × MIC) have also been considered to minimize the occurrence of microbiological failure and/or resistance.[48,49] In their study, Tam et al.[50] found that a Cmin/MIC ratio of 1.7 was more commonly associated with the emergence of resistant clones than a ratio of 6 during the treatment of *Pseudomonas aeruginosa*. In a recent Italian study, a steady-state concentration/MIC ratio of ≤5 was identified as

an independent predictor of microbiological failure in critically ill patients with Gram-negative bacillary infections.[51] Consistent findings were observed in clinical trials that specifically addressed infections with a high risk of clinical or microbiological failure, such as hospital-acquired pneumonia (VAP) caused by *P. aeruginosa* and *Klebsiella pneumoniae*. These trials demonstrated improved clinical outcomes with Cmin/MIC ratio targets of >4–5.[51–53] Notably, the use of a higher target ratio is based on the considerations of tissue diffusion and technical uncertainties pertaining to MIC and β-lactam concentration measurements.[54] However, only observational studies have demonstrated higher PK/PD targets to offer improved microbiological and clinical remission without any notable impact on mortality.[51,53]

Actual MICs are considered to define the therapeutic range in documented infections. The turnaround time remains the main issue with the use of MICs. Alternatives need to be considered in the early phases of infection, when the MIC of the causative pathogen is unclear. The epidemiological cut-off (ECOFF) value, based on local ecology and the "worst-case scenario MIC" is the most common alternative used in this context. The "worst-case scenario MIC" refers to the highest MIC of susceptible pathogens that can be covered by the considered antibiotic. However, such approaches underestimate the probability of target attainment compared to actual MICs.[55,56] Notably, even the standardized method accepts standard deviations of 1–2 dilutions on a 2-logarithmic series; this leads to some degree of variability in PK/PD target attainment. On comparing these alternatives, Smekal et al.[57] found that the ECOFF MIC is the most suitable alternative. Rapid diagnostic and rapid antimicrobial susceptibility testing may help reduce turnaround times in the future, and potentially aid better tailoring of antimicrobial therapy.

Increased loading doses

As any delay in initiating adequate antibiotic therapy worsens the prognosis of septic patients, adequate drug concentrations need to be achieved in the early phases of sepsis management. However, empirical standard dosing regimens lead to subtherapeutic concentrations of different classes of antibiotics.[58–60] As the Vd of antibiotics is often increased, higher loading doses are needed for hydrophilic antimicrobials (e.g., β-lactams, vancomycin, aminoglycosides, and colistin) to achieve similar and adequate therapeutic concentrations.[61–63] New optimal β-lactam loading doses have been suggested (8 g in 3 h for piperacillin, 4 g in 3 h for ceftazidime and cefepime, and 2 g in 0.5 h for meropenem) based on population PK analysis and Monte Carlo simulations (which have gained popularity for the optimization of antibiotic dosing regimens).[61] Similarly, higher than recommended loading doses have been proposed for vancomycin, aminoglycosides, and colistin; this approach has been supported by findings from clinical validation studies, which have shown improvements in PK/PD target attainment for all three of these antibiotics.[64–67] Notably, the loading dose should not be altered in patients with renal impairment or those receiving RRT. The development of dosing nomograms may help clinicians better tailor the initial dosing of certain antibiotics (such as aminoglycosides) based on total body weight and renal CL.[68]

Optimal mode of administration of antibiotics

Continuous infusion mode

Beta-lactam antibiotics have traditionally been administered via intermittent infusions. However, an increasing body of research suggests that continuous infusions may be more effective in specific clinical situations. Studies that evaluated the continuous administration of β-lactam antibiotics have demonstrated improved outcomes including a higher rate of PK/PD target achievement, higher clinical remission rates, and superior microbiological eradication.[69,70] However, three previous meta-analyses that included randomized controlled trials (RCTs) did not demonstrate continuous β-lactam antibiotic infusions to be superior to intermittent administration in terms of survival; in this context, it is worth noting that studies performed to date have been small and underpowered, even when pooled.[71–73] A more recent meta-analysis of individual patient data from multicenter RCTs that compared continuous and intermittent infusions of β-lactam antibiotics found the hospital mortality (censored at day 30) to be lower in the continuous infusion than in the intermittent infusion group (19.6% *vs*. 26.3%; relative risk=0.74; 95% confidence interval [CI]: 0.56 to 1.00, P=0.045).[74] The most recent RCT that compared outcomes between continuous and intermittent infusions of meropenem in a cohort of 607 critically ill patients found no significant difference in terms of all-cause mortality and the emergence of pandrug- or extensively drug-resistant bacteria at day 28.[75] The results of the BLING III trial, which compared outcomes between continuous and intermittent infusions of β-lactam antibiotics in 7000 patients, are pending and will provide further information regarding the impact of mode of administration on clinical outcomes.[76] The benefits of continuous infusions have also been investigated for non-β-lactam antibiotics. In this context, observational studies have shown that continuous infusions of linezolid achieved the PK/PD targets (AUC_{24}/MIC >80 and %T > MIC >85%) in patients with ARC, those who were obese, and those with elevated MICs (2–4 mg/L).[77] Continuous infusion of linezolid was also found to be associated with improved alveolar diffusion and better clinical outcomes, in terms of clinical improvement and mortality.[78,79] However, RCTs comparing both modes of administration are lacking.

Inhaled antibiotics

Inhaled antibiotics have emerged as a potential means of treating pulmonary infections while limiting the emergence of multidrug-resistant (MDR) strains. High doses of inhaled antibiotics need to reach the infected lung parenchyma to optimize outcomes. Mesh nebulizers and specific ventilator settings that require short-acting sedation should therefore be preferred to optimize lung deposition and prevent patient-ventilator asynchrony.[80] The clinical benefit of inhaled antibiotics has been evaluated in a pairwise/network meta-analysis that included eight observational studies and RCTs, each.[81] Patients treated with inhaled antibiotics demonstrated significantly higher rates of clinical recovery (risk ratio: 1.21, 95% CI: 1.09 to 1.34; P=0.001) and microbiological eradication (risk ratio: 1.42, 95% CI: 1.22 to 1.650; P <0.0001), with no difference in terms of mortality or risk of nephrotoxicity. Two recent RCTs, namely, the INHALE and VAPORISE trials, assessed the efficacy of inhaled antibiotics (aminoglycosides and fosfomycin)

as adjunctive therapy; they failed to demonstrate any benefit of the inhaled route over standard-of-care intravenous administration in the treatment of Gram-negative bacteria (GNB) related VAP.[82,83] These trials mainly assessed the use of inhaled antibiotics as adjunctive and not substitutive therapy. However, no non-inferiority RCTs have compared inhaled polymyxins to new intravenous cephalosporins/β-lactamase inhibitor antibiotics in patients with VAP caused by MDR GNB.

Another strategy relies on the use of inhaled antibiotics to prevent, rather than to treat, VAP. In this context, a recently published RCT assessed the benefit of a 3-day course of inhaled amikacin therapy (20 mg/kg ideal body weight) in preventing VAP in mechanically ventilated patients; the study demonstrated a significant reduction in the development of the first episode of VAP (15% in the amikacin group *vs.* 22% in the placebo group, P=0.004).[84]

Therapeutic drug monitoring (TDM) and dosing software

Between-patient variability in drug response represents a critical challenge in clinical practice, and considerably complicates the identification of patients who are most likely to obtain benefits and experience adverse effects. Different doses may need to be tested before the best "fit" is determined for a particular patient. However, this approach is time-consuming and may occasionally frustrate healthcare professionals. Various strategies have emerged over the past few decades to address these challenges. Dosing nomograms and TDM had initially been introduced as pioneering solutions for optimizing drug dosages. The concept of model-informed precision dosing (MIPD) is a recently developed innovative approach.

Three narrative reviews and one systematic review and meta-analysis have recently evaluated the compelling subject of TDM for β-lactam antibiotics in critically ill patients.[85–88] Two of these reviews focused on the effect of TDM on clinical outcomes, with particular emphasis on mortality rates and the emergence of antimicrobial resistance.[87,88] Notably, neither of these comprehensive reviews found a significant association between the use of TDM for β-lactam antibiotics and either mortality or the development of antimicrobial resistance. It is worth noting, however, that certain risks of bias, categorized as critical to serious in severity, may have influenced the findings. This bias was predominantly related to non-adherence to TDM recommendations, deviation from intended intervention, and confounding. Additionally, prospective RCTs were lacking in both these reviews and the studies primarily focused on special populations (septic patients with normal renal function, those with burns, and neutropenic patients).[89] Notably, patients receiving RRT and those exhibiting ARC were not included in these investigations; however, both these factors have considerable association with inappropriate β-lactam exposure.

In the most recent RCT, Hagel et al.[90] included a substantial sCle (n=249) from multiple centers. The study focused solely on the use of piperacillin for empirical therapy, and the PK/PD target was based on the MIC of *P. aeruginosa*. The primary outcome, namely, the difference in mean sequential organ failure assessment scores with and without TDM, did not demonstrate significance (P=0.39).[90] Although TDM lowered the mortality rate by 4.2%, and offered a higher rate of microbiological and clinical remission, these differences were not statistically significant. TDM offered better achievement of target concentrations, thereby resulting in less underdosing. However, the optimal target (without overdosing) was achieved in less than 50% of patients within the first 5 days, with the nadir occurring on the first day.[90] The authors of the study attributed the lack of mortality benefit to the high PK/PD target (particularly on the first day), which was based on a relatively high MIC of piperacillin (16 mg/L) for *P. aeruginosa*. However, as most identified bacteria had lower MIC values, failure to achieve the target did not lead to poor outcomes. Few studies have compared the setting of an *a priori* PK/PD target (based on a worst-case scenario with high MIC, mainly for empirical therapy) to *a posteriori* MIC, as determined after bacterial identification. In their study, Leon et al.[91] demonstrated an increase in PK/PD target attainment in critically ill patients with intra-abdominal infections, both before (33%) and after bacterial documentation (71%). This highlights the critical role of MIC selection in defining the PK/PD target for therapy.[92] A notable distinction between clinical studies and daily practice is the delay in obtaining TDM results, which are typically accessible within a few hours after sample collection in clinical studies. However, a recent survey on TDM practices in real-world healthcare settings has demonstrated the delay in response time to be a significant barrier, and has identified it to be the primary obstacle to the effective implementation of TDM.[93] The survey also identified the interpretation of TDM results to be a second major challenge, especially in non-expert centers. Two factors need to be prioritized to reduce discrepancies between clinical study findings and everyday clinical practice; these include the reduction of turnaround time for TDM results and the improvement of support for result interpretation.

Monitoring the side effects of antibiotics

A growing body of evidence highlights the potential for significant toxicity with β-lactam antibiotics, particularly in specific populations such as those in the ICU.[94] TDM is deemed to be essential for mitigating the risk of excessive β-lactam exposure, which leads to toxicities. Given that the thresholds for dose-dependent β-lactam toxicity are generally on the higher side, this approach allows for the initial use of higher empirical dosing regimens, which can then be revised based on TDM. Recent studies have demonstrated the pivotal role of TDM in minimizing non-β-lactam antimicrobial-related toxicity.[95] In a retrospective study that included 93 patients, higher-than-licensed doses based on TDM did not result in excessive drug toxicity for either meropenem or piperacillin-tazobactam; this was observed despite the administration of more than 40% higher mean daily doses in the high-dose groups.[96] Nevertheless, the absence of well-established toxicity thresholds for β-lactams represents a major challenge to the implementation of TDM-based dosing adjustments for limiting toxicity. Efforts to define toxicodynamic targets are therefore urgently needed. In this context, some studies have focused on the relationship between β-lactam concentrations and neurotoxicity in the intensive care setting. For instance, a study found cefepime trough concentrations of above 22 mg/L (when administered via intermittent infusions) or steady-state concentrations of above 35 mg/L (with continuous infusion) to be associated with neurotoxicity in 50% of patients.[97,98] Similar risks have been reported for trough concentrations exceeding 64 mg/L for meropenem, 125 mg/L

for flucloxacillin, and 360 mg/L for piperacillin (when not used with tazobactam).[99] In addition, a steady-state plasma concentration of piperacillin exceeding 157 mg/L (when administered in combination with tazobactam) has been found to be predictive of neurological disorders in ICU patients with a specificity of 97% and a sensitivity of 52%.[100] Notably, a study found that in cases where the minimum free concentration normalized to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoint for *P. aeruginosa* (i.e., fCmin/MIC *P. aeruginosa* ratio) exceeded a value of 8, approximately half of ICU patients treated with piperacillin/tazobactam and two-thirds of those treated with meropenem demonstrated a significant deterioration in neurological status.[101] In this context, an ongoing prospective clinical trial, namely, the OPTIMAL TDM study (NCT03790631), aims to establish toxicity thresholds for cefepime, imipenem, meropenem, piperacillin, flucloxacillin, amoxicillin, and ceftazidime. However, the potential impact of TDM-guided dosing adjustments on the prevention of β-lactam toxicity and improvement of clinical outcomes remains to be determined.

New and Old Antibiotics in Critically Ill Patients

Repositioning old antibiotics

There has been renewed interest in old antibiotics to address the increase in bacterial resistance to commonly used antibacterial drugs (Table 1). As some old antibiotics show in vitro activity against MDR bacteria, these drugs may represent an alternative approach to treating these infections. However, clinical indications and dosing recommendations described in the product information have not been revised and may not be appropriate for critically ill patients.[102]

Colistin

Different formulations and conventions are currently used to describe doses of polymyxins (international unit or mg of colistin base activity) worldwide; this leads to some uncertainties regarding their optimal use in the clinic. Unlike polymyxin B, colistin is administered intravenously, as the inactive prodrug colistin methanesulfonate sodium (CMS) is transformed into various derivatives before being converted to colistin. The time to achieve therapeutic plasma colistin concentrations is longer compared to that of polymyxin B. Studies have found high inter- and intra-individual variations in colistin PK, which result in highly variable plasma concentrations following administration of the same dosing regimen.[66,103–105]

International consensus guidelines have therefore provided therapeutic recommendations to guide the optimal clinical use of polymyxins.[106] A recent systematic review that included population PK studies and prospective clinical trials on colistin has also highlighted the need for individualized dosing regimens and TDM for critically ill patients, based on the narrow therapeutic index of the drug and wide inter-individual

Table 1
PK and dosing of repurposed antimicrobial agents.

Antimicrobial agents	Spectrum of activity	Dosing regimens in ICU	Factors affecting PK	Protein binding	PK/PD targets	TDM recommended
Colistin[106,107]	Enterobacterales MDR/XDR *Pseudomonas aeruginosa* MDR/XDR *Acinetobacter baumannii*	LD: 9 MUI* MD: 4.5 MUI/12 h	• Renal function • RRT -CVVHD-related CL: 41% for CMS, 28% for colistin CVVHD: LD 9 MUI, MD 3 MUI/8 h -CVVHDF: 50%	40%	$AUC24h_{ss}$/MIC=50 mg/h/L ⇔Css=2 mg/L (total drug) EUCAST susceptible breakpoint: ≤2 mg/L for EB, PA, AB CLSI breakpoint: *S* ≤2, *R* >4 mg/L ECOFF: 2 mg/L (EB, AB), 4 mg/L (PA)	Yes
Fosfomycin (combination therapy)[115,117–120]	MDR/XDR *Pseudomonas aeruginosa* MDR/XDR *Acinetobacter baumannii* ESBL-E NDM KPC	LD: 8 g MD: CI 16–24 g/24 h Alternative: 8 g/8 h over 1–4 h	• Renal function • RRT -CVVHD: 28.7% reduction in AUC 4 g/6 h if CrCl >90 mL/min 5 g/8 h if CrCl >50 mL/min 4 g/8 h in anuric patients -PIRRT: 5 g/8 h	Negligible	AUC_{0-24}/MIC ≥21.5 for CRE $fAUC_{0-24}$/MIC ≥40.8 for MDR PA EUCAST breakpoint: 32 mg/L, CLSI breakpoint: 64 mg/L ECOFF: 128 mg/L (KP), 256 mg/L (PA), 512 mg/L (AB)	Yes
Temocillin[122,125]	Enterobacterales: ESBL-E AmpC KPC	LD: 2 g MD: CI 6 g/24 h	• Renal function • RRT -IHD: IHD-related CL ~55% 1.5–3 g based on interdialytic period	~80%	EUCAST breakpoints: *S* ≤0.001 mg/L, *R* >16 mg/L ECOFF: 16 mg/L (*E. coli*), 8 mg/L (KP) for UTI	Yes for infections outside the urinary tract

* 1 million IU corresponds to ~33 mg CBA, and to ~80 mg of the chemical CMS.

AB: *Acinetobacter baumannii*; AmpC: AmpC cephalosporinase; AUC: Area under the curve; CI: Confidence interval; CL: Clearance; CLSI: Clinical & Laboratory Standards Institute; CMS: Colistin methanesulfonate sodium; CrCl: Creatinine clearance; Css: Steady-state concentration; CVVHD: Continuous veno venous hemodialysis; CVVHDF: Continuous veno venous hemodiafiltration; *E. coli*: *Escherichia coli*; EB: Enterobacterales; ECOFF: Epidemiological cut-off; ESBL-E: Extended-Spectrum BetaLactamases; EUCAST: European Committee on Antimicrobial Susceptibility Testing; ICU: Intensive care unit; IHD: Intermittent hemodialysis; KP: *Klebsiella pneumoniae*; KPC: *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales; LD: Loading dose; MD: Maintenance dose; MDR: Multidrug-resistant; MIC: Minimal inhibitory concentration; NDM: New Delhi Metallo BetaLactamases; PA: *Pseudomonas aeruginosa*; PD: Pharmacodynamics; PIRRT: Prolonged intermittent renal replacement therapy; PK: Pharmacokinetics; RRT: Renal replacement therapy; TDM: Therapeutic Drug Monitoring; UTI: Urinary tract infection; XDR: Extensively drug-resistant.

variability.[107] A CMS loading dose of 9 MIU (300 mg colistin base activity over 0.5–1 h has been recommended, followed by the administration of the first MD 12–24 h later. The international consensus guidelines have suggested adjustments to the MD based on renal function and TDM.[106] Notably, the conversion of the CMS fraction into colistin increases by 33%, 50%, and 67% for CrCl values of 120 mL/min, 50 mL/min, and 25 mL/min, respectively; this results in higher colistin concentrations among patients with impaired renal function. TDM is not widely available for colistin, as precautions need to be taken to ensure that sample collection, handling, and analysis are conducted appropriately to minimize *ex vivo* conversion of CMS to colistin. Preliminary data of TDM for CMS and colistin in critically ill patients show poor correlation between CMS and colistin concentrations; they also indicate a risk of both under and overdosing during the administration of guideline-based dosing regimens.[108] The use of colistin without TDM may be unsafe in critically ill patients (especially in those infected with pathogens that exhibit high MICs and having normal renal function).

Fosfomycin

The repurposing of fosfomycin combinations (based on its activity against MDR Enterobacterales and non-fermenting GNB) represents an important strategy for addressing the threat of antimicrobial resistance.[109–111] Fosfomycin is a hydrophilic drug which demonstrates low protein binding, low molecular weight, and extensive penetration into various tissues. Different intravenous formulations are available, and fosfomycin disodium is used in several countries other than the United States. However, several population PK studies have shown considerable intra- and inter-individual variability; the findings suggest that critically ill patients are exposed to inappropriate plasma concentrations when standard dosing is applied.[112–114] Experimental and in vitro studies on MDR pathogens have defined the 24-h area under the plasma drug concentration–time curve over the MIC ($AUC_{0–24}$/MIC) to be the best PK/PD index for fosfomycin.[115,116] Based on findings from Monte Carlo simulations, new dosing regimens involving prolonged and continuous infusions have been suggested to achieve optimal exposure in critically ill patients with carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *P. aeruginosa* infections and those undergoing RRT.[113,114,117–120] The use of prolonged infusion may also decrease the risk of fosfomycin-related severe hypokalemia.[121]

Temocillin

Temocillin, a 6-a-methoxy derivative of ticarcillin, is an old antibiotic that is licensed in different European countries (including the United Kingdom, Belgium, Luxembourg, and France) for infections of the urinary tract, bloodstream, and lower respiratory tract. Its use has been limited by issues related to clinical breakpoints and optimal therapeutic regimens. The EUCAST has recently defined clinical breakpoints exclusively for urinary tract infections (UTI) ($S \leq 0.001$, $R > 16$ mg/L); other sites of infection have been excluded from its recommendations due to the lack of clinical and PK data.

Despite these limitations, a renew of interest due to its restricted spectrum to Enterobacterales including bacterial activity against ESBL, AmpC, and KPC-producing Enterobacterales has emerged in the last years.

Available PK data in critically ill patients show high inter-individual variability and efficacy with a 6-g daily continuous infusion (after a 2 g loading dose) across various sites of infection.[122–124] A population PK analysis of temocillin (in plasma and epithelial lining fluid) from patients with severe pneumonia has shown a lung penetration ratio of 0.73; it also demonstrated higher target attainment with continuous infusions of temocillin. However, on administering the 6-g daily regimen, the breakpoints in plasma and epithelial lining fluid were found to be 2 mg/L for intermittent infusions and 4 mg/L for continuous infusions; these values are well below the breakpoint of 8 mg/L, which has been established for systemic infections.[123] In intra-abdominal infections, population PK analysis demonstrated a risk of underdosing in patients with ascites and preserved renal function.[124] Higher (continuous infusions of 8 g/day) dosing may be necessary to achieve PK/PD targets in this population; however, robust clinical data are needed for these cases.[124] Adjusted drug dosing is also required for critically ill patients who are receiving RRT.[125] Temocillin needs to be administered with caution for severe infections in sites other than the urinary tract. In addition, MIC determination and TDM should be considered to ensure optimal temocillin exposure in critically ill patients.

New antibiotics

New antimicrobial drugs have been developed over the past decade to address the threat of antimicrobial resistance. These mostly include combinations of a β-lactam and a β-lactamase inhibitor.

The preservation of such an armamentarium requires in-depth knowledge of the microbiological spectrum of activity, PK/PD properties, and clinical study results for each drug. Several recently published reviews have addressed these issues.[126–130] The characteristics of new antimicrobials that are used in critically ill patients are summarized in Table 2.[131–136]

Future Perspectives and Conclusion

Due to the considerable and frequently unpredictable variability in PK among critically ill patients, it is essential to adopt a personalized approach for antimicrobial dosing in this population. Although TDM is of value for making precise dose adjustments based on individual patient requirements, it is not universally available for most antimicrobial agents.[93] In addition, TDM does not provide guidance for initial empirical drug dosing, which has been demonstrated to have a significant impact on crucial outcomes (such as mortality in cases of septic shock). Clinicians therefore need to predict drug distribution patterns and the likelihood of achieving adequate drug concentrations at the infection site; this creates a particular challenge in the clinic. Clinical prediction is based on the complex interplay between patient physiological characteristics, underlying diseases, physicochemical properties of the drug, and the influence of any extracorporeal treatments used (Figure 1).

Several approaches are being investigated for better tailoring of antimicrobial drug doses in critically ill patients. At the early phase of sepsis, the rapid determination of the causative pathogen susceptibility profile and MIC, through rapid diagnostic tools is emerging and can quickly inform clinicians on the

Table 2
PK and dosing considerations of new antibiotics.

Antimicrobial agents	Spectrum of activity							Dosing regimens in ICU	Factors affecting PK	Protein binding	PK/PD targets
	ESBL	AmpC	KPC	OXA-48	NDM	XDR/MDR PA	XDR/MDR AB				
Ceftolozane tazobactam[131]	√	√	✗	✗	✗	√	✗	Pneumonia: 3 g/8 h Other sites: 1.5 g/8 h	• Renal function -ARC: 1.5 g LD, MD: 4.5 g/24 h CI -CrCl >50: 1.5–3 g/8 h -CrCl 30–50: 0.75–1.5 g/8 h -CrCl 15–29: 0.375–0.75 g/8 h -CrCl <15: LD 0.375–0.75 g, MD: 0.15–0.30 g/8 h • RRT IHD: LD 0.375–0.75 g, MD: 0.15–0.30 g/8 h CRRT: 0.5–1 g/8 h	21%/30%	30% fT > MIC 20% fT > CT of 1 mg/L
Ceftazidime avibactam[130]	√	√	√	√	✗	√	✗	2.5 g/8 h	• Renal function -ARC: NA -CrCl >50: 2.5 g/8 h -CrCl 31–50: 1.25 g/8 h -CrCl 16–30: 0.9375 g/12 h -CrCl 6–15: 0.9375 g/24 h • RRT IHD: 0.9375 g/48 h CRRT: 1.25 g/8 h	<10%/5%–8%	50% fT > MIC 50% fT > CT of 1 mg/L
Cefiderocol[132,133]	√	√	√	√	√	√	√	2 g/8 h over 2 h	• Renal function -ARC: 2 g/6 h -CrCl 60–120: 2 g/8 h -CrCl 30–59: 1.5 g/8 h -CrCl 15–29: 1 g/8 h -CrCl <15: 0.75 g/12 h • RRT -IHD: 0.75 g/12 h -CVVH: dosing adjusted to effluent rate 1 L/h: 1.5 g/12 h 2 L/h: 2 g/12 h 3 L/h: 1.5 g/8 h ≥4 L/h: 2 g/8 h	40%–60%	75% fT > MIC
Aztreonam avibactam[134]	√	√	√	√	√	√	✗	LD: 0.5 g/0.167 g MD: 1.5 g/0.5 g/6 h	NA	56%/8%	60% fT > MIC 50% fT > CT
Imipenem relebactam[126,135]	√	√	√	✗	✗	√	✗	1.25 g/6 h	• Renal function -CrCl 90–150: 1.25 g/6 h -CrCl 60–89: 1 g/6 h -CrCl 30–59: 0.75 g/6 h -CrCl 15–29: 0.5 g/6 h • RRT -IHD: 0.5 g/6 h -CRRT: NA	20%/22%	40% fT > MIC fAUC/MIC=7.5
Meropenem vaborbactam[130,136]	√	√	√	✗	✗	✗	✗	4 g/8 h over 3 h	• Renal function -CrCl >40: 4 g/8 h -CrCl 20–39: 2 g/8 h -CrCl 10–19: 2 g/12 h -CrCl <10: 1 g/12 h • RRT -CVVHD: 2 g/8 h	2%/33%	45% fT > MIC fAUC/MIC ≥18–24

AB: *Acinetobacter baumannii*; AmpC: AmpC cephalosporinase; ARC: Augmented renal clearance; AUC: Area under the curve; CI: Confidence interval; CrCl: Creatinine clearance; CT: Threshold of concentration; CVVH: Continuous venovenous hemofiltration; CVVHD: Continuous veno venous hemodialysis; ESBL-E: Extended-Spectrum BetaLactamases; ICU: Intensive care unit; IHD: Intermittent hemodialysis; KPC: *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales; LD: Loading dose; MD: Maintenance dose; MDR: Multidrug-resistant; MIC: Minimal inhibitory concentration; NA: Not available. NDM: New Delhi Metallo BetaLactamases; OXA-48: OXA-48 carbapenemase; PA: *Pseudomonas aeruginosa*; PD: Pharmacodynamics; PK: Pharmacokinetics; RRT: Renal replacement therapy; XDR: Extensively drug-resistant.

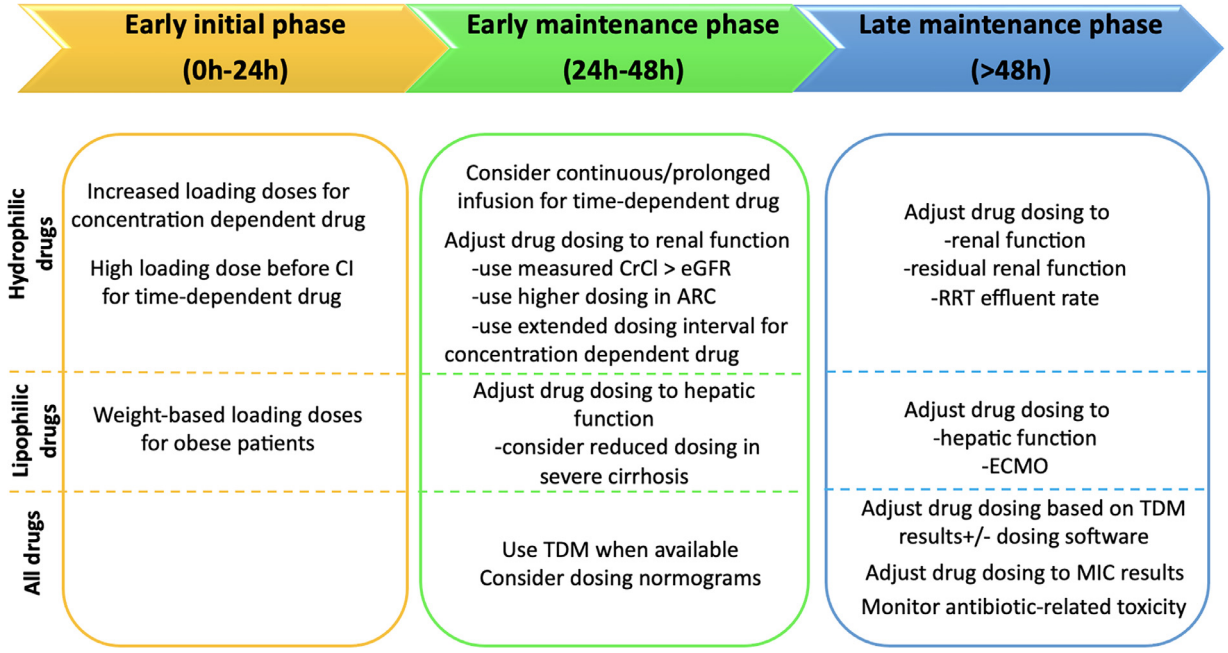
Early initial phase
(0h-24h)
Early maintenance phase
(24h-48h)
Late maintenance phase
(>48h)
Hydrophilic drugs
Increased loading doses for concentration dependent drug
High loading dose before CI for time-dependent drug
Consider continuous/prolonged infusion for time-dependent drug
Adjust drug dosing to renal function
-use measured CrCl > eGFR
-use higher dosing in ARC
-use extended dosing interval for concentration dependent drug
Adjust drug dosing to
-renal function
-residual renal function
-RRT effluent rate
Lipophilic drugs
Weight-based loading doses for obese patients
Adjust drug dosing to hepatic function
-consider reduced dosing in severe cirrhosis
Adjust drug dosing to
-hepatic function
-ECMO
All drugs
Use TDM when available
Consider dosing normograms
Adjust drug dosing based on TDM results+/- dosing software
Adjust drug dosing to MIC results
Monitor antibiotic-related toxicity

Figure 1. Drug dosing optimization across the antimicrobial course.
ARC: Augmented renal clearance; Cl: Clearance; CrCl: Creatinine clearance; ECMO: Extracorporeal membrane oxygenation; eGFR: Estimated glomerular filtration rate; MIC: Minimal inhibitory concentration; RRT: Renal replacement therapy; TDM: Therapeutic drug monitoring.

need for higher dosing regimens in case of resistant strains. In addition, MIPD has recently emerged as an approach for optimizing antimicrobial dosing in critically ill patients. It aims to improve therapeutic outcomes by achieving an optimal balance between efficacy and toxicity in the individual patient. The approach involves the application of mathematical and statistical algorithms that simultaneously integrate patient covariates (i.e., *a priori* prediction) and individual drug concentration measurements (i.e., *a posteriori* prediction or Bayesian forecasting). Although the use of these models is often perceived as sophisticated and complicated, they may be integrated into clinical practice via software tools. In addition to supporting clinical decision-making (regarding therapeutic individualization), they may improve bedside implementation. Preliminary studies have shown that the implementation of MIPD for vancomycin dose adaptation has helped reduce the incidence of vancomycin-associated nephrotoxicity; it was also found to be a cost-effective approach for preventing nephrotoxicity in patients with renal impairment.[95,137,138] In conclusion, well-designed prospective clinical trials are needed to determine the benefits of precision dosing for β-lactams.

Author Contributions

Claire Roger: Writing – original draft, Supervision, Methodology, Data curation, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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